REMARKS

Claims 1, 3, 4, and 18-27 are pending[1]. Claims 1, 3, 4, and 18 are rejected under 35 U.S.C. § 112, first paragraph. Applicants address each basis for rejection below.

The Specification

The specification has been amended to delete pages 16 and 17. Pages 16 and 17 contain a list of references. All of the references listed on pages 16 and 17 were included on an Information Disclosure Statement mailed on January 15, 1999 and copies of the references were enclosed with the Information Disclosure Statement. This amendment contains no new matter.

Claim Amendments

The term "G-CSF" has been replaced with "granulocyte colony stimulating factor" in claims 1, 18, 21, and 24. Support for this amendment is found, for example, at page 2, lines 5-10, and page 14, line 16, to page 15, line 3, of the English language specification. Claim 1 has also been amended to recite that the second polypeptide can be a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) of wild-type granulocyte colony stimulating factor receptor or a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) and

[1] The Office Action indicates that claims 1, 3, 4, and 18 are pending. Applicants submit that this is in error as Applicants' last reply also included claims 19-27 which had been previously presented and which were not canceled in the last reply.

amino acid residues 725 through 756 of wild-type granulocyte colony stimulating factor receptor. Support for this amendment is found, for example, at page 9, lines 16-24, of the English language specification. Further, claim 1 has been amended to recite a "blood" cell. Support for this amendment is found, for example, at page 7, lines 13-17, of the English language specification. In view of the amendment to claim 1, claims 18, 21, and 24 have also been amended. The present amendments contain no new matter.

Claims 3, 4, 19, 20, 22, 23, and 25-27 have been canceled. The present amendments have been made solely to expedite prosecution and Applicants reserve the right to pursue canceled subject matter in this or in a continuing application.

Objection to the Claims

The Office objects to claims 1 and 18 for reciting the term "G-CSF" without setting forth the corresponding definition. As noted above, the claims, as amended, replace the term "G-CSF" with its definition, namely "granulocyte colony stimulation factor."

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1, 3, 4, and 18 are rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of written description in the specification and for a lack of enablement. Applicants address these bases for rejection as they apply to the present claims, including claims 21 and 24, which, as noted above, should have been examined in the present

Office Action.

Written Description

The Office rejects claims 1, 3, 4, and 18 for failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The Office states (page 4):

> For purposes of examination, claim 1 has been construed as encompassing a very broad genus of fusion proteins wherein the "first polypeptide" of [s]aid fusion protein ...encompasses virtually any and all manner of "ligand binding domain of [any] steroid hormone receptor that, upon ligand binding, self-associates." The second polypeptide of the fusion protein has been interpreted as encompassing virtually any granulocyte colony stimulating factor receptor, or "proliferation inducing domain thereof that, upon self-association of said first polypeptide, imparts proliferation activity to [any] cell.

And further states (page 7):

> [G]iven the enormous breadth of the genus of fusion molecules encompassed by the rejected claims, and given the limited description from the instant specification of such fusion molecules, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus.
>
> Claims 3 and 4 have been canceled; the rejection of these claims is moot.

Applicants note that claim 1 (and its dependent claims), as amended, requires the first polypeptide to include an estrogen-binding domain of an estrogen receptor that, upon ligand binding, self-associates, and the second polypeptide to include a granulocyte colony stimulating factor receptor, a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) of wild-type granulocyte colony stimulating factor receptor, or a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) and amino acid residues 725

through 756 of wild-type granulocyte colony stimulating factor receptor that, upon self-association of the first polypeptide, imparts proliferation activity to a blood cell. The fusion proteins encompassed by the present claims find adequate support in the specification as filed to meet the written description requirement.

In particular, in Example 1, Applicants describe constructing a chimeric protein including "the entire G-CSF receptor and the ligand (estrogen)-binding domain of the estrogen receptor ["GCRER"]" (see e.g., page 9, lines 12-14). As such, a fusion protein having a first polypeptide including an estrogen-binding domain of an estrogen receptor and the second polypeptide including a granulocyte colony stimulating factor receptor ("GCR") is described in the specification as filed.

In addition, for example, at page 9, lines 16-20, the specification teaches construction of a mutant of the GCRER fusion protein that is deficient in the 5th residue, Glu, through the 195th residue, Leu, of the granulocyte colony stimulating factor receptor ("GCRΔ(5-195)/ER"). Further, for example, at page 9, lines 21-24, the specification describes a GCRER fusion protein that, in addition to lacking residues 5-195, lacks residues 725-756 ("GCRΔ(5-195, 725-756)/ER"). Accordingly, the specification as filed also describes fusion proteins having a first polypeptide including an estrogen-binding domain of an estrogen receptor and either a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) of wild-type granulocyte colony stimulating factor receptor ("GCRΔ(5-195)"), or a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) and amino acid

residues 725 through 756 of wild-type granulocyte colony stimulating factor receptor ("GCRΔ(5-195, 725-756)"). On this basis alone, there can be no question that one skilled in the art would recognize that Applicants were, at the time of filing, in possession of the fusion proteins encompassed by the claims.

Moreover, Example 2 of the specification teaches:

> Proliferation of IL-3-independent and estrogen-dependent cells was observed in 7 out of 11 wells where "pCMX-GCRER" was introduced, in 3 out of 3 wells where "pCMX-GCRΔ(5-195)/ER" was introduced, and in 52 out of 52 wells where "pCMX-GCRΔ(5-195, 725-756)/ER" was introduced.

Further, the specification, in Example 6, teaches:

> Among the bone marrow cells infected with "vMXGCRER" or "vMXGCRΔ(5-195)/ER," granulocyte-macrophage lineage colonies and erythroblast lineage colonies, which had differentiated from the bone marrow cells by the estradiol stimulation, were observed.

Clearly, the specification describes fusion proteins that impart proliferation activity to a blood cell that expresses it. Thus, Applicants' specification also describes that the presently claimed fusion proteins have the function required by the claims.

Finally, the Office asserts that the specification does not "provide adequate written description of any amino acid sequence that is associated with any of the stipulated functions or activities of the various components." Applicants, in the last reply, provided evidence that the sequences of a GCR and an estrogen receptor were known in the art at the time the application was filed[2]. The claims, as amended, are directed to fusion

[2] Fukunaga et al., Cell 61:341-350, 1990; Fukunaga et al., EMBO J. 10:2855-2865, 1991; and Greene et al., Science 231:1150-1154, 1986.

proteins containing a GCR (or specific mutants) and an estrogen-binding domain of an estrogen receptor. Given that the sequence of a GCR was known at the time of filing, one skilled in the art would recognize whether a fusion protein contains a GCR sequence or the particular mutant GCR sequences recited in the claims. Similarly, the structure of the estrogen receptor was known in the art at the time the application was filed.

The Federal Circuit has indicated that § 112 does not impose a *per se* rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field. *Capon v. Eshhar,* 418 F.3d 1349, 1360, 76 U.S.P.Q. (BNA) 1078 (Fed. Cir. 2005). The Federal Circuit, in reversing the Board's conclusion that the written description requirement necessitated a listing of the specific nucleotide sequences of the claimed DNA, stated:

> The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes. (Emphasis added.)

Capon, 418 F.3d at 1358.

The written description requirement must be applied in the context of the particular invention and the state of the knowledge in the art. Applicants submit that the specification need not describe estrogen receptor and GCR sequences known in the art at the time of filing to meet the written description requirement for the present claims.

In sum, Applicants' specification describes constructing the claimed fusion

proteins using known sequences and describes expressing these fusion proteins in a blood cell where expression results in proliferation activity. As such, one skilled in the art, in view of the specification, would reasonably conclude that Applicants were in possession of the claimed invention at the time of filing. The written description rejection of claims 1, 18, 21, and 24, as amended, should be withdrawn.

Enablement

Claims 1, 3, 4, and 18 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. As noted above, claims 3 and 4 have been canceled and the rejection of these claims is moot. The Office states (page 12):

> [T]he specification ...[does] not teach that all elements of the fusion protein were well know[n], that the properties requires [sic] of the components of the fusion protein will be retained and have the desired effect (induce cell proliferation) under any conditions.

And further states (page 14):

> None of these examples [Examples 1-6] are directed to the use of any one of the constructs in any method that would have utility. Additionally, the specification is essentially silent is [sic] showing that the components of the fusion protein would in fact have the desired activities and functionalities when combined and used.

Applicants submit that claims 1, 18, 21, and 24, as amended, are free of this basis of rejection.

As noted above, the specification, for instance in Example 2, teaches that expression of a fusion protein containing an estrogen receptor hormone binding domain and GCR, GCRΔ(5-195), or GCRΔ(5-195, 725-756) in a cell results in estrogen-dependent proliferation. Moreover, Example 6 of the specification teaches selectively

proliferating granulocyte-macrophage lineage cells and erythroblast lineage cells expressing GCRER or GCRΔ(5-195)/ER from bone marrow cells by estradiol stimulation. Consequently, the specification teaches how to make and use the fusion proteins encompassed by the present claims to selectively proliferate a blood cell lineage.

The specification, as noted above, discloses the specific reagents recited in the present claims as well as the conditions under which the reagents have the required function. Thus, as taught, for example, at page 15, lines 5-13, the specification enables one skilled in the art to make and use the fusion proteins of the present invention to selectively amplify blood cells, for example, in gene therapy. For all the above reasons, Applicants submit that claims 1, 18, 21, and 24, as amended, are free of the enablement rejection. This basis for rejection should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested. Nonetheless, if there are any remaining issues, Applicants respectfully request a teleconference with the Examiner to bring this case into condition for allowance.

Enclosed is a Petition to extend the period for replying to the final Office Action for two (2) months, to and including May 2, 2006, and a check in payment of the required extension fee.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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James D. DeCamp, Ph.D.
Reg. No. 43,580

JAN N. TITTEL, PH.D.
Reg. No. 52,290

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045